

lactic use of whole blood may well be used routinely in such cases immediately after birth.

I am very enthusiastic in favor of the prophylactic forceps operation aided by episiotomy in the presence of a rigid pelvic floor with a long and moderately narrowed angle. Properly used it protects the delicate brain tissues of the baby, avoids the danger of undue shock and cerebral hemorrhage and also conserves the maternal strength. One should always exercise a studied slowness and gentleness in every forceps operation, whether it is a prophylactic procedure or one designed to terminate a prolonged labor with fetal embarrassment. Skill and not force is the requirement in these cases. Too often serious cerebral trauma is inflicted by the compression of forceps blades which may be prevented by gauze interposed between the forceps handles; or it may be caused by too forcible and unskillful downward traction which drags the head against the pelvic angle.

Posterior positions require all the skill and assistance that the obstetrician can utilize to protect the child and the mother. When progress is at all delayed I am in favor of manual assistance for securing dilatation of the cervix, followed by rotation and forceps extraction of the baby. While many of these cases will undoubtedly correct themselves and deliver spontaneously if left alone, it means usually a very prolonged and exhausting labor for the mother and for the baby a delivery that is endangered by shock and cerebral trauma. Such a procedure saves hours for the two patients and lessens their dangers.

As Doctor Silverberg emphasizes, prevention is the most important factor in treating these complications. The use of whole blood intramuscularly often accomplishes wonders, but if we can avoid the complication by skill and assistance, so much the better for these little patients.

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JOHN C. DEMENT, M.D. (2525 Fourth Street, San Diego)—Doctor Silverberg's article places a timely emphasis on a condition which is only too often overlooked. The diagnosis is easy only in the frank cases. Those that are more or less masked and appear late are not so easily recognized. These occur usually with hemorrhagic disease, the birth history is often normal, and symptoms may not appear until a bloody stool is seen. In these cases prolonged bleeding time is generally found, and the traumatic element may be slight. As in the cases developing earlier, blood transfusion, using whole or citrated blood, offers prompt relief if done in time.

The author stresses the intramuscular injection of blood. I am inclined to think that the Sidbury method of giving the blood intravenously through the umbilical stump is preferable, especially in urgent cases. If the cord is cut long, as it should be after difficult labors or in suspected cases, the blood may be given directly into the umbilical vein as late as three days after birth. In this way the blood is introduced directly into the circulation, which may be so weak that the intramuscular blood would never be absorbed. Alpha lobelin and carbon dioxide and oxygen mixtures are valuable aids in the treatment of these cases and are preferable to oxygen alone. In extreme cases the blood may be introduced into the fontanelle or directly into the ventricles.

There is very little one might add to the author's comprehensive discussion of the subject. His remarks on the prophylaxis of this condition are especially worthy of careful attention. The question of when and when not to interfere is an ever present one in obstetrics that demands our most careful judgment. As we begin to better recognize these cases of intracranial hemorrhage in the newborn, it appears that there is such a thing as occasionally being too cautious and that certain of these complications may be due to non-interference as well as to instrumental deliveries. Doctor Silverberg has certainly contributed something of decided value in presenting the subject from the viewpoint of the obstetrician.

## THE VAN DEN BERGH TEST AND THE ICTERUS INDEX\*

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AND

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DISCUSSION by Roy W. Hammack, M.D., Los Angeles; Charles L. Bennett, M.D., Los Angeles; Arthur L. Bloomfield, M.D., San Francisco.

THE study of pathological conditions associated with disturbed liver function has been considerably facilitated recently by the use of certain tests designed to determine the presence and the quantity of bilirubin in the blood in normal or pathological amounts. This paper considers two of these tests, namely, van den Bergh's and Meulengracht's.

### EARLY TESTS FOR BILIRUBIN IN BLOOD

Prior to van den Bergh various workers had considered the question of bile in normal blood. Hammerstein in 1878, by oxidation of a chloroform extract of serum, found that most bloods gave a blue or green color like that obtained from bilirubin by the same means. But his method was not delicate enough to detect small quantities with certainty and did not exclude the possibility that other colored compounds, not due to bilirubin, were formed by the reagents employed.

Aube, in 1908, introduced a spectroscopic method by means of which he was able to demonstrate bilirubin in most normal sera. The method is specific for bilirubin and useful as a control, but it is not easily used for quantitative determinations and, because of the large amount of blood required, is not suitable for clinical purposes.

Ehrlich, in 1883, discovered the diazo reaction, which goes by his name, and showed that of all the known bile pigments only bilirubin coupled with diazonium salts in acid solution. But Ehrlich did not work with blood serum.

### VAN DEN BERGH'S DIRECT AND INDIRECT TESTS

It was left to van den Bergh to show that Ehrlich's reaction could be employed for the detection of bilirubin in serum, exudates and other protein-rich fluids by a test requiring but little time to do, of great simplicity and of extraordinary delicacy and certainty. Van den Bergh says that the delicacy of the test is such that one part of bilirubin in one and a half million parts of serum can be easily demonstrated and that its specificity can be proved by control chemical tests and by the spectroscope.

Van den Bergh published his observations in 1918 in an extensive monograph entitled "Der Gallenfarbstoff im Blute." The test is, as he says, extremely simple. Briefly it consists in adding freshly prepared diazo reagent, either directly to the clear serum or to the protein-free supernatant fluid, after precipitation by means of two volumes of alcohol, whereupon a red or violet red color

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appears the depth of which is in proportion to the bilirubin content.

Fresh bile from the gall bladder and serum from patients with obstructive jaundice give the test in the first manner spoken of and also in the second manner. Normal serum and serum from patients with non-obstructive jaundice do not give the test in the first manner but do give it in the second manner. We have, therefore, two ways of doing the van den Bergh test: one known as the direct, the other as the indirect, by means of which we can distinguish between obstructive and non-obstructive jaundice.

Normal serum, when the indirect reaction is used, is found to contain as an average, one part of bilirubin in 500,000 parts of serum. All cases of jaundice of what ever sort can be shown by one test or the other to contain an increased amount of bilirubin; and a subnormal amount has been shown in aplastic anemia, secondary anemia, nephritis and in tuberculosis not complicated by emphysema.

Van den Bergh determined the normal content of serum by comparison with pure bilirubin in alcoholic solution. But since pure bilirubin is not easy to obtain, some other color standard had to be devised if the method was to be practical. Such a standard was found by van den Bergh, first in an ethereal solution of ferric thiocyanate and, later, in a water solution of cobaltous sulphate matching the color obtained from a dilution of one part of bilirubin in 200,000 parts of serum. Taking this depth of color as the unit of measurement van den Bergh showed the normal bilirubin content to be from 0.3 to 0.6 of a unit. The threshold for visible icterus has been found to be about two units and that for bile in the urine, about four units, though these relations are sometimes reversed. We have, therefore, in this fairly broad zone of "latent icterus" between 0.6 of a unit and 4.0 units, a method for the demonstration of a pathological increase of pigment at an earlier stage of disease than was heretofore possible.

#### SIGNIFICANCE OF VAN DEN BERGH'S TEST

Van den Bergh and others, particularly McNee, have dwelt on the theoretical deductions from these discoveries. It is beyond the scope of this paper to go further into the matter than to point out that two different bilirubin reactions are presented, the direct and the indirect, indicating that bilirubin exists in the blood stream in two different physical or chemical states. It is only fully elaborated bile, the product of normal liver cells and a normal reticulo-endothelial system, which gives the direct reaction; and this reaction is found, clinically, only when obstruction has occurred with consequent reabsorption of bile. That physical or chemical state of bilirubin which can be demonstrated only by the indirect reaction appears to be bilirubin, which is bound to a protein molecule and which, clinically, has failed of complete elaboration somewhere between its hemoglobin origin and the final state of free bile. Such failure may be presumed to be due to damaged polygonal cells of the liver lobule, or to

overloading of these cells and the cells of the reticulo-endothelial system by the products of excessive blood destruction. We may note here that the bilirubin produced locally in conditions such as hematomas, pleural and abdominal hemorrhages is demonstrable only by the indirect reaction.

#### MCNEE'S CLASSIFICATION OF JAUNDICE

Basing his suggestion on the view that the Kupffer cells of the reticulo-endothelial system elaborate bile pigment, and that the polygonal cells of the liver are chiefly concerned with its passage into the bile capillaries, in which passage, however, the bilirubin is affected in some way as indicated by van den Bergh's work, McNee suggests the following as the best classification of jaundice in the present state of our knowledge:

1. Obstructive hepatic jaundice.
2. Toxic and infective hepatic jaundice.
3. Hemolytic jaundice.

#### TECHNIQUE OF VAN DEN BERGH'S TESTS

The technique of van den Bergh's test and some of its modifications, such as that of Tannhauser and Andersen, which is the most important, is available in the literature and need not be given here. Our brief account of the method is not meant to cover working directions. Our difficulty in the application of the test has been that of others, namely, the uncertainty of getting a sufficiently close agreement in tint between the test taken, and the standard. We have found that slight adjustment of reaction by means of minimal additions of alcohol-ammonia, too small to affect quantitative relations, improves the matching of color and enables us to read the result with confidence and consistency within the limits of colorimetric determinations. This point is made by van den Bergh, but seems to have escaped most English translators and commentators.

#### MEULENGRACHT'S ICTERUS INDEX TEST

The other test to which we refer is Meulengracht's, announced by him in 1921 and popularized in this country by Bernheim, who gave to it the convenient name, Icterus Index. For the purpose of this test, Meulengracht assumes that the yellow color of serum is due to its bilirubin content, and he estimates this content by comparison with an artificial standard consisting of a 1:10000 solution of potassium bichromate in water. He takes this standard to indicate fifteen color units, and on this scale finds that normal serum has an index of from one to five such units; that the "first degree of jaundice" (latent jaundice) is encountered between five and ten on the scale, and visible from ten up.

Meulengracht's standard is easy to make, keeps well in the dark, and dilutions of normal and icteric serum match with it, ordinarily, very well. The preparation of the standard solution is not absolutely necessary, since an accurate colored disk for the colorimeter can be had. Serum for

TABLE 1—*Obstructive Cases with Visible Jaundice*

No.	Diagnosis	Van Den Bergh:		Ict.-Ind.	Remarks
		Direct	Indirect		
1	Catarrhal Jaundice	Positive	15.5	34	
2	Cholelithiasis	"	8.8	46	Operated on
3	"	"	Positive	30	" "
4	"	"	"	37, 68	
5	Cholecystitis Adhesions	Delayed	"		
6	Carcinoma Pancreas Diabetes	Positive	15.6 20.5	120	Blood Sugar 361 mg.
7	Ca. Stomach Liver Metastasis	Positive	4.4	25	
8	Ca. Stomach Liver Metastasis	"	9.8	75	Biopsy
9	Carcinoma Pancreas	"	35—	48	

this test must be perfectly clear and free from any trace of hemolysis.

#### REPORTS OF CASES

These are the two tests we have used in the cases reported on in this paper, out of a larger number from which some omissions had to be made because of insufficient clinical data. We have charted the cases as follows, viz.:

1. Obstructive cases with visible jaundice.
2. Cases of latent jaundice.
3. Hemolytic cases.
4. Miscellaneous cases in which study of liver function was indicated.

TABLE I

A glance at this table shows that we found a positive direct van den Bergh reaction in all cases of obstruction, as has been the experience of all other observers in such cases; and likewise a high icterus index. The high icterus index was strong presumptive evidence that the hypercoloration of the serum was due to bilirubin; practically sufficient evidence in certain of the cases but not positive proof since, conceivably, it might have been due to lutein, carotin, or other of the lipochromes normally or frequently found in serum in varying quantity. The van den Bergh test by virtue of its chemical specificity settled that point and, further and what is of more importance, by the form of the reaction, namely, the direct, showed

TABLE 2—*Cases without Visible Jaundice*

No.	Diagnosis	Van Den Bergh:		Ict.-Ind.	Remarks
		Direct	Indirect		
10	Chronic Cholecystitis	Positive	Faint	13.6	Dye-X-ray
11	" "	Negative	0.9	10.00	" "
12	" "	Weak delayed	Weak positive	10.00	" "
13	" "	Negative	1.4	8.8	" "
14	Cirrhosis of Liver	Weak delayed	1.4	8.8	Wassermann Neg.
15	" "	Negative	0.9	6.3	

that the cause of the hyperbilirubinemia was obstruction.

TABLE 2

The second table shows that both tests offered help in cases of latent jaundice, the van den Bergh always being in some degree positive and the icterus index always above normal. It is interesting to see that in a case of cirrhosis of the liver, a second test two months after the first showed a less strongly positive van den Bergh and a lower icterus index concomitant with clinical improvement from duodenal drainage. Here in this group of cases, and presumably in others, one test may be as good as the other, after the hypercoloration is proved by van den Bergh's test to be due to bilirubin and not to some other pigment.

TABLE 3

The third table shows a group of pernicious anemia cases. All of these were clinically typical and some of them extreme, with red cell counts as low as 500,000 and hemoglobin as low as 15 per cent. In one of the patients five tests were made during the course of treatment (by transfusion) and in this patient, as may be seen in the table (19 to 23 inclusive), the van den Bergh reaction varied from time to time in agreement with apparent clinical improvement and improved blood picture. Three of the cases were seen in remission and, as the table shows, might have been mistaken for secondary anemia if seen in this stage for the first time and if dependence had been placed on the blood count and the color index. The indirect van den Bergh reaction at once classified them correctly, as pernicious anemia. It is in this group of cases, namely, hemolytic icterus from whatever cause, that we encounter the form of bilirubin which gives a positive indirect reaction without a positive direct reaction. The icterus index was invariably high in all cases in this group including the three seen in remission.

TABLE 4

In the fourth table are shown eighteen cases of various conditions in which liver dysfunction or damage or a hemolytic process was suspected, partly because of a high icterus index which had been found previously in all of them. The peculiar value of the van den Bergh test is manifested in this group by its exclusion of liver damage or hemolytic process in certain of the cases in spite of the high icterus index. Case 31 is illustrative; clinical symptoms gave reason for suspecting disturbance of liver function and the icterus index was high. The van den Bergh reaction, however, was negative—that is to say, normal. The correctness of the van den Bergh reaction was tested in this patient by another highly sensitive method for the detection of liver damage, namely, Rosenthal's dye test, the result of which was the excretion of the dye as follows: present after five minutes, 5 per cent; after fifteen minutes, a trace only; after half an hour, none—in other words, a normal result in agreement with the van den Bergh reaction. The ultimate diagnosis in this patient was chronic appen-

dicitis, a conclusion which has been justified by several months' observation since these tests were made.

Case 35 is another one in point. The van den Bergh reaction was negative, but on the basis of clinical symptoms and a high icterus index a diagnosis of chronic cholecystitis was made; at operation the next day the gall bladder was found to be normal. It was a case of chronic appendicitis.

Three cases in this fourth table suggest that the icterus index was right and the van den Bergh test wrong, namely, cases 32, 33 and 36, or at least that the icterus index method was successful in indicating liver pathology and the van den Bergh test failed. Plainly this is true so far as the failure of the van den Bergh test is concerned in these three cases, but a glance at a larger number of cases in this group in which the two tests did not agree will show that a high icterus index is sometimes merely incidental and suggests that it may have been so in these cases. It is a fact that the van den Bergh test gives us little or no help in the group of toxic and infective jaundice cases, the common run of cases in which help would be most desired. This is its shortcoming. On the other hand the icterus index carries with it the danger of "false positives," and perhaps more so in this part of the world where we are permitted such a full and varied diet.

The direct van den Bergh reaction was negative in all cases in the fourth group as would be expected since obstruction was not in question in any of them.

The secondary anemia cases in the fourth table show negative direct reactions and either normal or subnormal indirect reactions, in agreement

TABLE 3—*Hemolytic Cases*

No.	Diagnosis	Van Den Bergh:		Ict.-Ind.	Remarks
		Direct	Indirect		
16	Pernicious Anemia	Negative	1.5	42	
17	" "	"	8.3		Red cells 525,000 Hemoglobin 32
18	" "	"	2	15	
19	" "	"	4.8	30	Red cells 7,000 Hemoglobin 18
20	" "	"	2.4	10.7	Transfusion 5 days previously. Red cells 120,000 Hemoglobin 23
21	" "	"	Positive	15	Red cells 2,020,000 Hemoglobin 48
22	" "	"	2.9	12.5	Red cells 1,880,000 Hemoglobin 38
23	" "	"	1.4	21	Red cells 1,970,000 Hemoglobin 38
24	" "	"	Positive	7.5	Red cells 2,020,000 Hemoglobin 48
25	" "	"	2.5	16.6	Red cells 1,570,000 Hemoglobin 38
26	" "	"	1.1		In remission: Red cells 3,800,000 Hemoglobin 67 Color index 0.9
27	" "	"	2.3	10	Red cells 2,100,000 Hemoglobin 60
28	" "	"	0.9	10	In remission.

TABLE 4—*Miscellaneous*

No.	Diagnosis	Van Den Bergh:		Ict.-Ind.	Remarks
		Direct	Indirect		
29	Flagellatae Infection	Negative	Normal	15	
30	" "	"	"	10.7	Red cells 4,330,000 Hemoglobin 85
31	Chronic Appendicitis	"	"	15	Rosenthal dye test
32	" "	"	"	17	Operated on: Appendicitis and 1 stone in thickened gall bladder.
33	Chronic Cholecystitis	"	"	12	
34	Syphilitic Hepatitis	"	1.6	12.5	Wassermann 4+
35	Chronic Cholecystitis	"	Normal	15	Operated on: Gall bladder normal Chronic appendicitis
36	Liver Cirrhosis	"	"	10.7	
37	History of Malaria	"	2.8	15	Mild jaundice Urobilinogen in urine.
38	" "	"	3.3	12	Red cells 4,500,000 Hemoglobin 90
39	" "	"	2.9	15	
40	Secondary Anemia	"	Normal	12.5	Red cells 2,210,000 Hemoglobin 40
41	" "	"	Below Normal	7.5	Red cells 2,800,000 Hemoglobin 55
42	Chronic Nephritis Secondary Anemia	"	"	6.24	Red cells 2,530,000 Hemoglobin 42
43	Acute lymphatic Leukemia	"	Normal		
44	Hodgkins disease	"	"		
45	Addison's disease	"	"	8	
46	No definite symptoms	"	"	12	Red cells 4,280,000 Hemoglobin 85

with the reported findings of others; the differentiation from pernicious anemia is very clear.

Three cases included in the fourth table are there chiefly because of their clinical interest: one a case of acute lymphatic leukemia which came to autopsy; one a case of Hodgkin's disease; and one a case of Addison's disease. As was to be expected all three gave negative van den Bergh reactions.

## SUMMARY

A series of cases is reported comprising (1) obstructive visible jaundice, in which the van den Bergh test and the icterus index agree; (2) latent jaundice cases, in which the two tests agree; (3) pernicious anemia cases, showing the same agreement; (4) a variety of clinical cases, in some of which the two tests did not agree.

## CONCLUSIONS

On the basis of the work here reported we conclude (1) that both van den Bergh's test and Meulengracht's test (the icterus index) are of clinical value; (2) that, whatever its shortcomings, the van den Bergh test is not misleading; (3) that the icterus index, since it does not distinguish between bilirubin and other substances

which color blood serum, may be misleading unless it is controlled by the van den Bergh test or some other specific test for bilirubin; (4) that the van den Bergh test is an aid to the differentiation between obstructive and non-obstructive jaundice, in which respect the icterus index is of no assistance.

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#### DISCUSSION

ROY W. HAMMACK, M. D. (1003 Pacific Mutual Building, Los Angeles)—Doctors Segall and Terry have given us an interesting and instructive comparison of these two tests for bile pigment in the blood. All will agree, I believe, that the van den Bergh test gives us more information than the icterus index though at the cost of somewhat more effort.

I was surprised to see in the report so many instances of high icterus index in which the presence of bilirubin was not shown by the van den Bergh test. This emphasizes the importance of controlling the high icterus index by a specific test for bilirubin. Provided it is so controlled I believe that the icterus index is a more accurate quantitative test and is more easily performed than the quantitative van den Bergh.

Our knowledge of jaundice has been greatly increased by the study of the blood by these methods and this comparative study is no small contribution to that knowledge.

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CHARLES L. BENNETT, M. D. (607 South Hill Street, Los Angeles)—This paper by Segall and Terry calls attention to a particularly valuable quantitative test for bilirubin in the blood stream. Jaundice means increased bilirubin in the blood, and the proper interpretation of the amount and kind means much in exact diagnosis of forms of anemia and obstructive diseases of the biliary ducts. The indirect test is always positive when bilirubin is present in the blood stream and is valuable in differentiating pernicious anemia with its extensive destruction of red blood cells. When bilirubin passes through the polygonal hepatic cells its molecular structure is changed and here the direct van den Bergh test is positive and, when present, indicates resorbed and molecularly changed bilirubin due to biliary duct obstruction. Attention should be called to the fact that jaundice of the "invisible variety" (*i. e.*, before becoming evident to ordinary sight) can be diagnosed. Also the van den Bergh is not a mere color test as is the icterus index. The latter gives a positive reaction with other pigments, while the van den Bergh is a definite chemical reaction for bilirubin, with all the advantage accruing from the fact that it cannot be confounded with any other substance. This paper is timely in its emphasis of a specific procedure, harmless for the patient, and simple for the clinician.

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ARTHUR L. BLOOMFIELD, M. D. (Stanford University School of Medicine, San Francisco)—Doctor Segall's and Doctor Terry's observations are in accord with those of other workers. In regard to the value of the two tests for the detection of hyperbilirubinemia there is now quite general agreement that the van den Bergh is more delicate and accurate. Whenever this can be performed it is undoubtedly the method of

choice, and the icterus index should be reserved as a simpler and a less accurate method. The technical difficulties connected with the van den Bergh test are, however, considerable, and unless the procedure is performed with the greatest care, it may be more satisfactory to employ the simpler though less accurate method.

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DOCTOR SEGALL (closing)—Regarding the relatively large number of cases showing a high icterus index as against no abnormal quantity of bilirubin by the van den Bergh test in the same case, this is precisely what we want to bring out: that the van den Bergh test is a specific qualitative and quantitative test for bilirubin. The icterus index is not specific for bilirubin. The only way possible at present to correct misleading returns by the icterus index method, is by use of the van den Bergh test, properly done. We therefore consider the icterus index as less accurate. As to technical difficulties in doing the van den Bergh test, we have been able to overcome them.

### LIPIODOL—ITS USE IN PULMONARY SUPPURATIONS\*

By E. RICHMOND WARE, M. D.

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DISCUSSION by William C. Voorsanger, M. D., San Francisco; Ernest H. Falconer, M. D., San Francisco; A. L. Bramkamp, M. D., Banning.

A SATISFACTORY clinical and anatomical diagnosis in a large number of suppurative conditions of the lungs has always been a difficult problem. Lung abscess and bronchiectasis are frequently suspected from the history alone, and physical and routine roentgenological examinations usually give valuable additional information. However, the accurate localization of the pathology and the discovery of all the involved areas have often been impossible, with the result that attempts at treatment by the various methods at our command have not been very encouraging. In lipiodol, or iodized oil, we have a non-irritating fluid substance which can be safely introduced into the tracheobronchial tree. It is opaque to the x-ray and will clearly demonstrate the outline of intrapulmonary cavitation in the bronchi themselves, or in the various portions of the lung parenchyma which have direct connection with the larger bronchi.

#### LIPIODOL

Lipiodol is a golden yellow, oily substance, fairly viscid, becoming more fluid at body heat, with a content of 40 per cent metallic iodine. The iodine is in a close combination with the oil of poppy seed and fails to give the usual starch reaction. It has a characteristic odor, and on standing undergoes decomposition, with the liberation of free iodine, as indicated by the appearance of a brownish tint. Such a specimen is unfit for use.

#### HOW LIPIODOL IS USED

In addition to its use in the respiratory tract it has been employed to demonstrate the spinal canal, the vas deferens, the seminal vesicles, the patency of the fallopian tubes, the size and character of

\* Read before the California Medical Association Section on General Medicine at the Fifty-Sixth Annual Session, Los Angeles, April 25-28, 1927.